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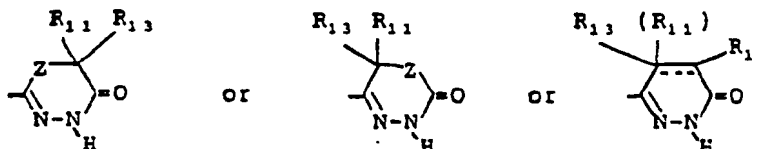
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Heterocyclic compounds.

New heterocyclic compounds of formula I



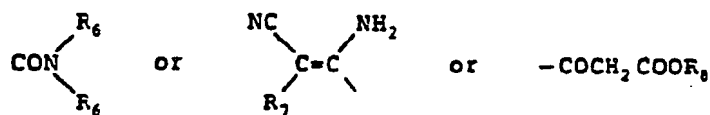
In which Het means one of following groups;



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wherein R_{11} , R_{13} and R_{14} mean independently hydrogen, hydroxymethyl or lower alkyl group, Z means S, O or NH; A means valency bond, $-\text{CH}=\text{CH}-$, or $-\text{CH}_2-\text{CH}_2-$ group; R_1 and R_2 independently mean nitro, cyano, halogen, amino, carboxamido, aryl, aroyl, pyridyl, alkoxycarbonyl, acyl or one of following groups;



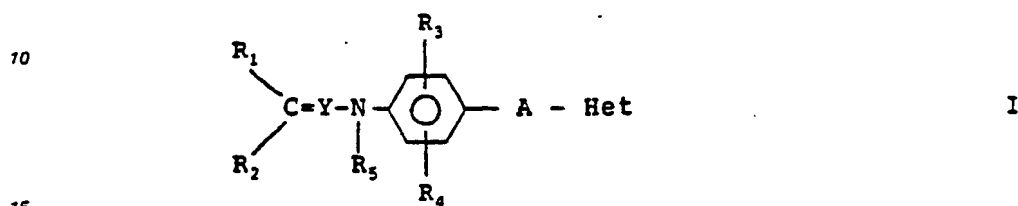
wherein R_6 means hydrogen or lower alkyl group, R_8 means lower alkyl, R_7 means cyano or COOR_{10} , wherein R_{10} means hydrogen or lower alkyl or R_1 and R_2 together form a substituted or unsubstituted 5 or 6 membered ring which may contain 1 or 2 heteroatom N; R_3 , R_4 , and R_5 mean independently hydrogen, hydroxy or lower alkyl group; Y means N or CH. The compounds may be used in the treatment of congestive heart failure.

Heterocyclic compounds

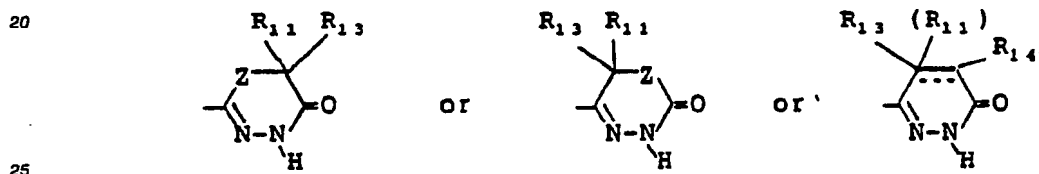
The present invention relates to new heterocyclic compounds and salts thereof as well as new intermediates. The invention also relates to compositions containing these compounds and to a process for the preparation of the same.

The present compounds are useful as cardiotonic agents, antihypertensive agents and vasodilators for the treatment of congestive heart failure. The compounds are new.

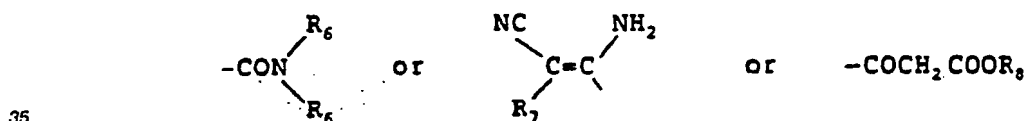
The new compounds according to the present invention are heterocyclic compounds of formula I



wherein Het means one of following groups;



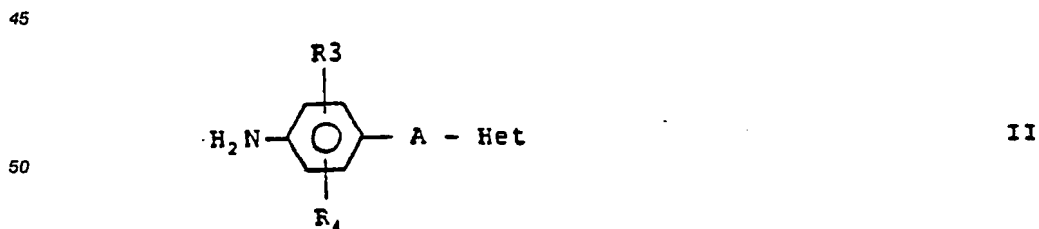
wherein R_{11} , R_{13} and R_{14} mean independently hydrogen or lower alkyl group, Z means S, O or NH; A means valency bond, $-\text{CH}=\text{CH}-$ or $-\text{CH}_2-\text{CH}_2-$ group; R_1 and R_2 independently mean nitro, cyano, halogen, amino, carboxamido, aryl, aroyl, pyridyl, alkoxycarbonyl, acyl or one of following groups;



wherein R_6 means hydrogen or lower alkyl group, R_8 means lower alkyl, R_7 means cyano or COOR_{10} , wherein R_{10} means hydrogen or lower alkyl or R_1 and R_2 together form a substituted or unsubstituted 5 or 6 membered ring which may contain 1 or 2 heteroatom N; R_3 , R_4 , and R_5 mean independently hydrogen, hydroxy or lower alkyl group; Y means N or CH.

The compounds according to formula I may be prepared in accordance with the following reaction sequences.

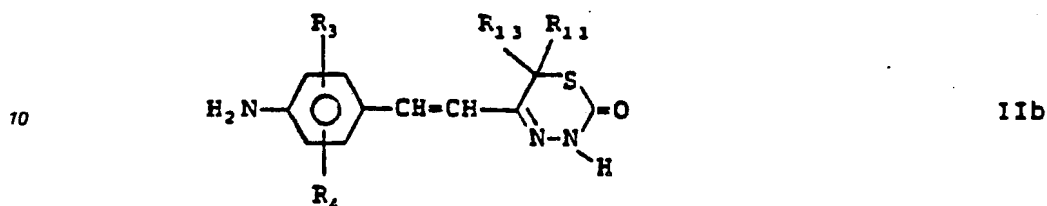
The intermediates according to formula II



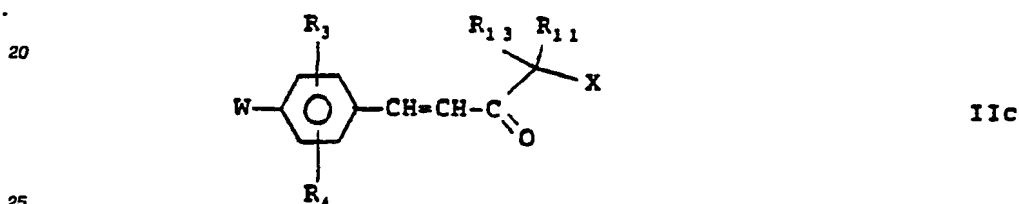
wherein R_3 , R_4 , A and Het are the same as defined before, may be prepared according to the methods known in the literature, for example in European Patent Application No. 52442, in U.S. Patent No. 4,656,170 and in J. Med. Chem., 17, 273-281 (1974).

The new intermediates of formula IIb

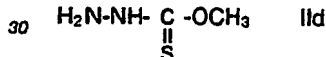
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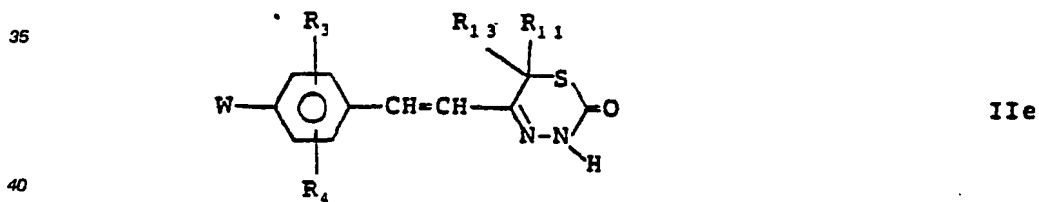
15 wherein R_3 , R_4 , R_{11} , and R_{13} are the same as defined before, may be prepared by reacting the compound of formula IIc (3. Org. Chem., 28, 2446-2447, 1963, Hudson, R. et al.)



wherein R_3 , R_4 , R_{11} , R_{13} are the same as defined before, W is nitro or acetamido group and X is halogen, with the compound of formula IIc (J. Liebigs Ann. Chem. 791-799, 1977, Ege, G. et al.)

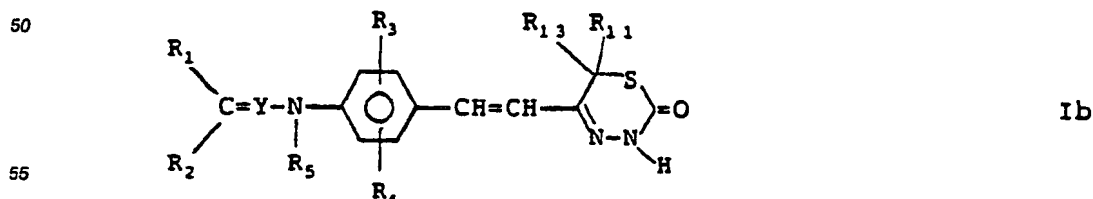


in an inert solvent at elevated temperature to form compounds according to formula IIe



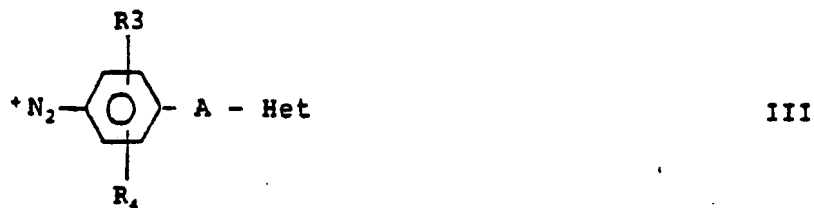
wherein R_3 , R_4 , R_{11} , R_{13} and W are the same as defined before, after which the nitro group is reduced or the acetamido group is hydrolyzed to form compounds IIb, where R_3 , R_4 , R_{11} and R_{13} are the same as defined before.

Compounds of formula IIb may be used in the preparation of compounds according to formula I having the structure Ib



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_{11} , R_{13} and Y are as defined before.

A compound of formula II is treated with nitrous acid to form the diazonium compound having formula III



wherein R₃, R₄, A and Het are the same as defined before. The diazonium compound III is then allowed to react with a compound having an activated methylene group of formula IV



wherein R₁ and R₂ are the same as defined before, in acidic conditions at lowered temperature to give compounds according to formula I in accordance with the present invention.

Alternatively the compounds I according to the present invention may be prepared by condensation of a compound having formula V



35 wherein R₃, R₄, R₅, A and Het are the same as defined before, with a compound having formula VI



wherein R₁ and R₂ are the same as defined before, in an inert solvent at normal or elevated temperature to give the compounds in accordance with formula I according to the present invention.

45 Compound V may be prepared from compound III according to the methods known in the literature (FI patent application 863564 or European patent application No. 223937).

Alternatively compounds I according to the present invention where Y is CH may be prepared by allowing compounds II to react with a compound having formula VII



where R₁ and R₂ are the same as defined before and R₁₅ is a lower alkyl group in an inert solvent at normal or elevated temperature to give the compounds in accordance with formula I according to the present invention.

Compounds IV and VI are either commercially available products or may be prepared according to the methods known in the literature.

The compounds of formula I according to the present invention where R_5 is lower alkyl group may also be prepared by alkylation of the compounds I, where R_5 is hydrogen, with alkylhalide in an inert solvent and in the presence of an inorganic or organic base.

The term "alkyl" as employed herein by itself or as part of another group includes both straight and branched chain radicals of up to 18 carbon atoms, preferably 1 to 8 carbon atoms, most preferably 1 to 4 carbon atoms. The term "lower alkyl" as employed herein by itself or as part of another group includes both straight and branched chain radicals of 1 to 7, preferably 1 to 4, most preferably 1 or 2 carbon atoms. Specific examples for the alkyl and lower alkyl residues, respectively, are methyl, ethyl, propyl, isopropyl, butyl, tert. butyl, pentyl, hexyl, octyl, decyl and dodecyl including the various branched chain isomers thereof.

The term "acyl" as employed herein by itself or as part of another group refers to an alkylcarbonyl or alkenylcarbonyl group, the alkyl and alkenyl groups being defined above.

The term "aryl" as used herein by itself or as part of another group refers to a monocyclic or bicyclic group containing from 6 to 10 carbon atoms in the ring portion. Specific examples for aryl groups are phenyl, naphthyl and the like. "Aroyl" means in a corresponding way an arylcarbonyl group.

The term "alkoxy" as employed herein by itself or as part of another group includes an alkyl group as defined above linked to an oxygen atom.

The term "substituted" as used herein in connection with various residues refers to halogen substituents, such as fluorine, chlorine, bromine, iodine or trifluoromethyl group, amino, alkyl, alkoxy, aryl, alkyl-aryl, halogen-aryl, cycloalkyl, alkylcycloalkyl, hydroxy, alkylamino, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, or alkylthio substituents.

The "substituted" groups may contain 1 to 3, preferably 1 or 2, most preferably 1 of the above mentioned substituents.

Salts of the compounds, when applicable, may be prepared by known methods. Physiologically acceptable salts are useful as active medicaments, however, preferred are the salts with alkali or alkaline earth metals.

The compounds according to this invention are formulated into dosage forms using the principles which are known to a person having average skills in the art. The compounds according to this invention are given to a patient as such or in combination with suitable pharmaceutical excipients in the form of tablets, dragees, capsules, suppositories, emulsions, suspensions or solutions whereby the contents of the active compound is in the formulation from about 1 to 100 % per weight. Choosing suitable ingredients for the formulation is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds and other ingredients normally used in this field of technology may be also used.

The compositions are given enterally or parenterally, the oral way being the easiest and preferred way.

The compositions are formulated depending upon the purpose of the medicine, normal uncoated tablets being quite satisfactory. Sometimes it is advisable to use coated tablets, i.e. so-called enterotables, to secure that the medicine reaches the desired part of the gastrointestinal tract. Dragees and capsules may be used too.

In a conventional way it is possible to make formulations which liberate the active ingredient slowly during a prolonged period of time.

It is also possible to give the desired dose of the medicine using suppositories. Suppositories are also given when the desired systemic effect is desired with patients having nausea and the like symptoms.

The present compounds may be given alone or in a combination with other medicines.

Congestive heart failure is characterized by the decrease in cardiac output and by the increase in right and left ventricular filling pressure. These hemodynamic conditions can produce symptoms of dyspnea, fatigue and edema.

Treatment of congestive heart failure usually focuses on the three principle factors determining cardiac performance: preload, impedance (afterload) and contractility. Vasodilation can improve cardiac function by reducing preload and/or afterload. Cardiac output can be increased directly by augmenting contractility.

The severity of congestive heart failure is usually classified by the New York Heart Association categories; Class I, II, III or IV. The therapeutic benefits of decreases in preload and afterload or increases in contractility may vary among both classes and individual patients. Therefore, it may be advantageous to have compounds which produce varying degrees of vasodilation and increase in contractility.

At the moment a series of compounds the mechanism of which is based on the phosphodiesterase isozyme III (PDE_{III}) inhibition are in clinical trials for the treatment of congestive heart failure. These

compounds increase the contractility of the cardiac muscle and produce vasodilatation. However, it is possible that the long-term application of those compounds leads to calcium overload in the cardiac muscle, which could trigger arrhythmias. The vasodilation based on the PDE_{III} inhibition is an advantage and thus it was desired also that the present compounds would be PDE_{III} inhibitors. Nevertheless, the main mechanism to increase cardiac contractility should be a mechanism which does not produce calcium overload. The enhancement of the turnover of intracellular calcium released from sarcoplasmic reticulum and the increase of calcium sensitivity of contractile proteins are such mechanisms which do not induce calcium overload.

The contraction in cardiac muscle and in vascular smooth muscle is triggered by the binding of calcium to troponin and to calmodulin, respectively. In order to get increase of cardiac muscle contraction and to avoid vasocontraction troponin has been chosen as a target of the present compounds. Thus the main screening method was the measurement of retention times of the compound in troponin high-performance liquid affinity chromatography (HPLAC) column using mobile phase without calcium (EDTA solution in table 1) or with 30 mM calcium (Ca²⁺ solution in table 1) to find out the calcium dependent binding to troponin. Commercially available troponin was coupled to the matrix of SelectiSpher-10TM Activated Tresyl silica HPLAC column (size 10 cm x 5 mm). The compounds were run through the column with the flow rate 1 ml/min and detected by UV-spectrophotometrically.

The PDE_{III} inhibition was studied by using enzyme preparation isolated from dog and guinea-pig heart according to Alajoutsijärvi and Nissinen (Anal. Biochem. 165, 128-132, 1987). The results of the studies are presented in table 2.

The cardiotonic action of the compound was studied in isolated, electrically driven, right ventricular papillary muscle of guinea-pig. In order to compare the cardiotonic action based on PDE_{III} inhibition to that based on the other mechanisms the experiments were carried out in normal Tyrode's bathing solution (Otani et al., Japan. J. pharmacol. 45, 425, 1987) and also in the solution with carbachol to eliminate the cardiotonic action due to the PDE_{III} inhibition (Alousi & Johnson, Circulation, 73 (suppl. III), 10-23, 1986). In some of the experiments the extracellular calcium was removed to demonstrate that the present compounds do not function by changing the calcium entry into the cell and that the site of action of the compounds is really located inside the cell and not on the cell membrane (Table 3.). The same was verified by using calcium entry blocker verapamil in the bathing solution.

The results show that the compounds according to the invention have significant calcium dependent binding to troponin compared to the reference compounds (Table 1.) The existence of the mechanism which is independent on the extracellular calcium was confirmed by investigating the ability of the compounds to induce tonic contraction in guinea-pig papillary muscle in the absence of extracellular calcium. In order to confirm that this intracellular mechanism is not related to the PDE_{III} inhibition carbachol was tested to shift the dose-response curves of the compounds. The present compounds have at least one cardiotonic mechanism of action which is not related to the inhibition of PDE_{III} enzyme, because the dose-response curves of some compounds were not shifted to the right in the presence of carbachol (Table 3.). The ability of the present compounds to induce a tonic contraction in the absence of extracellular calcium (Table 3.) shows that the PDE-independent mechanism is the enhancement of the turnover of calcium released from sarcoplasmic reticulum and/or the increase of calcium sensitivity of contractile proteins. Additionally, the present compounds are also more potent PDE_{III} inhibitors in dog and guinea-pig heart muscle than the reference compounds (Table 2.).

Table 1.

RETENTION TIMES OF THE COMPOUNDS IN TROPONIN-HPLAC COLUMN			
Compound of	Ca ²⁺ solution	EDTA solution	Ratio Ca ²⁺ /EDTA
Example 6	4.8 min	2.7 min	1.78
Example 1	3.5 min	2.2 min	1.59
Example 7	5.4 min	4.2 min	1.29
Example 33	6.6 min	3.9 min	1.69
Example 41	10.5 min	4.8 min	2.19
Example 43	2.4 min	1.2 min	2.00
Example 45	2.1 min	0.9 min	2.33
Example 49	18.4 min	8.0 min	2.30
milrinone	1.2 min	1.2 min	1.00
adibendan	14.8 min	15.0 min	0.99
pimobendan	70.4 min	79.6 min	0.88
MCI-154	6.4 min	12.4 min	0.52

Table 2.

INHIBITION OF CARDIAC PHOSPHODIESTERASE III		
	IC ₅₀ -value (μM)	
Compound of	Dog	Guinea-pig
Example 6	0.062	0.006 0.024 0.017 0.024 0.051 0.44
Example 7	0.23	
Example 1	0.27	
Example 33		
Example 41		
Example 43		
Example 49		
Example 44		
MCI-154	0.42	0.44
milrinone	0.58	
adibendan	1.00	
pimobendan	1.75	

Table 3.

CARDIOTONIC EFFECTS OF COMPOUNDS IN GUINEA-PIG PAPILLARY MUSCLE				
	A	B	Ratio	C
Compound of	EC ₅₀ , μM	EC ₅₀ , μM	B/A	
Example 6	0.17	0.16	0.94	yes
Example 7	0.74	2.7	3.6	*
Example 1	1.8	3.6	2.0	yes
Example 33	0.30			yes
Example 41	0.12			yes
Example 44	1.1			yes
Example 49	1.1			yes
milrinone	0.36	5.5	15.3	no
pimobendan	3.3			no
A = experiments carried out with carbachol B = experiments carried out in the presence of 10 μM carbachol C = ability to induce tonic contraction in the absence of extracellular calcium; drug concentration 100 μM				

* precipitation occurs at 100 μM concentration

The invention is illustrated but not limited by following Examples:

Example 1

6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

To a solution containing 0.95 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one and 2.5 ml of concentrated hydrochloric acid in 37.5 ml of water 0.38 g of sodium nitrite in 2.5 ml of water was added while stirring and cooling (0-5 °C). After 10 min 0.33 g of malononitrile in 2.5 ml of water was added. The solution was stirred for 1.5 h at room temperature after which the pH was adjusted to 6.0 with sodium acetate solution. The product was filtered, washed with water and ethanol. Yield 1.25 g, mp 283 °C.

Example 2

6[4-(1,1-dicyanomethylidenehydrazino)phenyl]pyridazin-3(2H)one

0.36 g of 6-(4-aminophenyl)pyridazin-3(2H)one was treated with sodium nitrite and malononitrile as described in Example 1. yield 0.45 g, mp > 300 °C.

Example 3

6-[4-(1-cyano-1-ethoxycarbonylmethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

0.37 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and ethyl cyanoacetate as described in Example 1. Yield 0.5 g, mp 235-239 °C.

5 Example 4

6-[4-(1,1-dicyanomethylidenehydrazino)-2-hydroxyphenyl]-4,5-dihydropyridazin-3(2H)one

10 0.4 g of 6-(4-amino-2-hydroxyphenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.2 g, mp 168-171 °C.

Example 5

15

6-[4-(1-cyano-1-(N,N-diethylaminocarbonyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

0.5 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and N,N-diethylcyanoacetamide. Yield 0.29 g, mp 200-205 °C.

20

Example 6

25

6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one

0.2 g of 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.25 g, mp 258-263 °C.

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Example 7

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6-[4-(1,1-diacetylmethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

0.45 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and 2,4-pentanedione as described in Example 1. Yield 0.7 g, mp 218-223 °C.

40

Example 8

6-[4-(1-ethoxycarbonyl-1-nitromethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

45

0.57 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and ethyl nitroacetate as described in Example 1. Yield 0.90 g, mp 237-241 °C.

50 Example 9

6-[4-(1-acetyl-1-(N,N-diethylaminocarbonyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

55

0.5 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and N,N-diethylacetoacetamide. Yield 0.26 g, mp 257-262 °C.

Example 10

6-[4-(1-ethoxycarbonyl-1-(4-pyridyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

5

0.57 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and ethyl 4-pyridyl acetate. Yield 0.67 g, mp 225-230 °C.

10 Example 11

6-[4-(1,1-bis(ethoxycarbonyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

15

0.38 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and diethyl malonate as described in Example 1. Yield 0.4 g, mp 175-178 °C.

Example 12

20

6-[4-(1-acetyl-1-ethoxycarbonyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

0.5 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and ethyl acetoacetate as described in Example 1. Yield 0.34 g, mp 110-115 °C.

25

Example 13

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6-[4-(2,6-dioxo-1-cyclohexylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

0.38 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and 1,3-cyclohexanedione as described in Example 1. Yield 0.6 g, mp 253-256 °C.

35

Example 1440

6-[4-(3,5-dimethyl(4-pyrazolidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

0.38 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and 3,5-dimethylpyrazole as described in Example 1. Yield 0.4 g, mp 315-318 °C.

45

Example 15

6-[4-(1,1-bis(ethoxycarbonyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

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A solution containing 0.60 g 6-(4-hydrazinophenyl)-4,5-dihydropyridazin-3(2H)one hydrochloride and 0.45 g of diethyl ketomalonate in 10 ml of 50 % ethanol was stirred for 3 h at room temperature. Water was added and the product was filtered and washed with water. Yield 0.35 g, mp 176-178 °C.

55

Example 16

6-[4-(1-acetyl-1-phenylmethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

0.5 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and 3-phenyl-2-butanone as described in Example 1. Yield 0.12 g, mp 113-118 ° C.

5

Example 17

10 6-[4-(1-chloro-1-ethoxycarbonyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

0.38 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and ethyl 2-chloroacetoacetate as described in Example 1. Yield 0.45 g, mp 225 ° C.

15

Example 18

20 6-[4-(1-carboxamido-1-cyanomethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

0.57 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and cyanoacetamide as described in Example 1. Yield 0.79 g, mp > 350 ° C.

25 Example 19

6-[4-(1-acetyl-1-benzoylmethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

30 0.57 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and 4-phenyl-2,4-butanedione. Yield 0.29 g, mp 195-198 ° C.

Example 20

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6-[4-(1-cyano-1-(2-pyridyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

40 0.57 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and 4-pyridylacetonitrile. Yield 0.83 g, mp 279-283 ° C.

Example 21

45

6-[4-(1,1-diacetylmethylidenehydrazino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one

0.4 g of 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and 2,4-pentanedione as described in Example 1. Yield 0.6 g, mp 194-196 ° C.

50

Example 22

55 6-[4-(1-amino-1-carboxamidomethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

The compound prepared in Example 17 was dissolved in conc. ammonia and stirred for 5 hours at room temperature. The product was filtered, washed with water and dried. Mp 260-266 ° C.

Example 23

6-[4-(2,2-bis(ethoxycarbonyl)vinyl)aminophenyl]-4,5-dihydropyridazin-3(2H)one

A solution containing 0.38 g of 6-(4-aminophenyl)-4,5-dihydro pyridazin-3(2H)one and 0.45 g of diethyl ethoxymethylenemalonate in 5 ml of dry ethanol was refluxed for 1.5 h. After cooling the product was filtered and washed with ethanol. Yield 0.3 g, mp 164 °C.

Example 24

6-[4-(2,2-dicyanovinyl)aminophenyl]-4,5-dihydropyridazin-3(2H)one

A solution containing 0.38 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one and 0.3 g of ethoxymethylenemalononitrile in 5 ml of ethanol was refluxed for 1 h. Yield 0.25 g, mp 290-295 °C.

Example 25

6-[4-(2,2-diacetylvinyl)aminophenyl]-4,5-dihydropyridazin-3(2H)one

A solution containing 0.38 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one and 0.4 g of 3-ethoxymethylene-2,4-pentanedione in 5 ml of ethanol was refluxed for 1 h. Yield 0.3 g, mp 218-222 °C.

Example 26

6-[4-(1-ethoxycarbonyl-1-ethoxycarbonyl(acetyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)-one

0.37 g of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and 0.43 g of diethyl 3-ketoglutarate as described in Example 1. Yield 0.75 g, mp 174-181 °C.

Example 27

6-[4-(1,1-dicyanomethylidene-N-methyl(hydrazino))phenyl]-4,5-dihydropyridazin-3(2H)one

A solution containing 0.28 g of the compound described in Example 1, 0.16 ml of methyl iodide and 0.2 g of potassium carbonate was refluxed for 6 hours. The solvent was evaporated and ethanol followed with water were added. Mp 247-250 °C.

Example 28

6-[4-(2-amino-1,1,3-tricyanopropenylidene)hydrazinophenyl]-4,5-dihydropyridazin-3(2H)one

0.37 g of 6-[4-aminophenyl]-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and 0.28 g of 2-amino-1-propenyl-1,1,3-tricarbonitrile as described in Example 1. Yield 85%, mp >300 °C.

Example 29

6-[4-(1,1-dicyanomethylidene-N''-methyl(hydrazino))phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one

A solution containing 0.28 g of the compound described in Example 6, 0.16 ml of methyl iodide and 0.2 g of potassium carbonate was refluxed for 6 hours. The solvent was evaporated and 2 ml of ethanol followed by 5 ml of water were added. The product was filtered and dried. Yield 0.2 g, mp 161-165 °C.

Example 30

6-[4-(2-amino-1,3-dicyano-3-methoxycarbonylpropenylidene)hydrazinophenyl]-4,5-dihydropyridazin-3(2H)one

0.37 g of 6-[4-aminophenyl]-4,5-dihydropyridazin-3(2H)one was treated with sodium nitrite and 0.35 g of methyl 3-amino-2,4-dicyanocrotonate as described in Example 1. Yield 0.5 g, mp >300 °C.

Example 31

6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydro-4-methylpyridazin-3(2H)one

0.44 of 6-(4-aminophenyl)-4,5-dihydro-4-methylpyridazin-3(2H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.3 g, mp 240-245 °C.

Example 32

2-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-5,6-dihydro-1,3,4-oxadiazin-5(4H)one

0.76 g of 2-(4-aminophenyl)-5,6-dihydro-1,3,4-oxadiazin-5(4H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.65 g, mp 350 °C (decomp.).

Example 33

(E)-6-[2-(4-(1,1-dicyanomethylidenehydrazino)phenyl)ethenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one

0.23 g of 6-[2-(4-aminophenyl)ethenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.3 g, mp 195-200 °C.

Example 34

(E)-6-[2-(4-(1,1-dicyanomethylidenehydrazino)phenyl)ethenyl]-5-methylpyridazin-3(2H)one.

0.47 g of 6-[2-(4-aminophenyl)ethenyl]-5-methylpyridazin-3(2H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.6 g, mp 325 °C (decomp.).

Example 35

6-[2-4-(1,1-dicyanomethylidenehydrazino)phenyl]ethyl]-4,5-dihydro-5-methylpyridazin-3(2H)one.

0.45 g of 6-[2-(4-aminophenyl)ethyl]-4,5-dihydro-5-methylpyridazin-3(2H)one was treated with sodium

nitrite and malononitrile as described in Example 1. Yield 0.59 g, 153-157 °C.

Example 36

6-[2,5-dimethyl-4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one

0.48 g of 6-(4-amino-2,5-dimethylphenyl)-4,5-dihydro-5-methylpyridazin-3(2H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.6 g, mp 197-199 °C.

Example 37

6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-5-methylpyridazin-3(2H)one.

0.2 g of 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.2 g, mp 265-273 °C.

Example 38

6-[4-(1,1-dicyanomethylidene-N-methylhydrazino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one.

0.28 g of 6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one (Example 6), 0.16 ml of methyl iodide and 0.2 g of potassium carbonate in 10 ml of acetone was refluxed for 6 h. The solvent was evaporated in vacuo and the residue was treated with 50 % ethanol-water. The product was filtered, yield 0.2 g, mp 161-165 °C.

Example 39

6-[4-(1-cyano-1-carbamidomethylidenehydrazino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one.

0.48 g of 6-(4-aminophenyl)-4,5-dihydro-5-methylpyridazin-3(2H)one was treated with sodium nitrite and cyanoacetamide as described in Example 1. Yield 0.66 g, mp 261-265 °C.

Example 40

4-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-phtalazin-1-(2H)one.

0.23 g of 4-(4-aminophenyl)phtalazin-1(2H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.25 g, mp 350 °C (decomp.).

Example 41

5-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-5,6-dihydro-6-methyl-1,3,4-thiadiazin-2(3H)one

0.25 g of 5-(4-aminophenyl)-5,6-dihydro-6-methyl-1,3,4-thiadiazin-2(3H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.29 g, mp 225-229 °C.

Example 42

2-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-5,6-dihydro-1,3,4-triazin-5(4H)one

5

0,19 g of 2-(4-aminophenyl)-5,6-dihydro-1,3,4-triazin-5(4H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0,24 g, mp > 350 ° C.

10 Example 43

6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydro-5-methyl-1,2,4-triazin-3(2H)one

15

1.5 g of 6-(4-aminophenyl)-4,5-dihydro-5-methyl-1,2,4-triazin-3(2H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.9 g, mp > 350 ° C (decomp.).

Example 44

20

5-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-5,6-dihydro-1,3,4-thiadiazin-2(3H)one

25

0.28 g of 5-(4-aminophenyl)-5,6-dihydro-1,3,4-thiadiazin-2(3H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.21 g, mp 210-215 ° C.

Example 45

30

6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydro-1,2,4-triazin-3(2H)one

35

0.3 g of 6-(4-aminophenyl)-4,5-dihydro-1,2,4-triazin-3(2H)one was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.41 g, mp. > 350 ° C (decomp).

Example 46

40

5-[2-(4-nitrophenyl)ethenyl]-5,6-dihydro-1,3,4-thiadiazin-2(3H)one

45

A solution containing 11.2 g of 1-chloro-4-(4-nitrophenyl)-2-oxo-3-butene (J. Org. Chem. 28, 2446, 1963) and 6.8 g of hydrazinecarbothioic acid O-methylester in 200 ml of acetonitrile was refluxed for 3 h. The crystals were filtered and washed with acetonitrile and ether. Yield 7.7 g (59%), mp. 231-240 ° C.

Example 47

50

5-[2-(4-aminophenyl)ethenyl]-5,6-dihydro-1,3,4-thiadiazin-2(3H)one

55

To a solution containing 7.5 g of 5-[2-(4-nitrophenyl)ethenyl]-5,6-dihydro-1,3,4-thiadiazin-2(3H)one (Example 46) in 300 ml of pyridine 18.0 g sodium dithionite in 150 ml of water was gradually added. The mixture was refluxed for 5 h. The organic phase was separated and evaporated to dryness in vacuo. The residue was treated with water and the product was filtered. Yield 4.0 g (60%), mp. 188-196 ° C.

Example 48

5-[2-(4-acetamidophenyl)ethenyl]-5,6-dihydro-1,3,4-thiadiazin-2(3H)one

A mixture containing 4.0 g of 1-chloro-4-(4-acetamidophenyl)-2-oxo-3-butene (J. Org. Chem., 28, 2446, 1963) and 2.3 g of hydrazinecarbothioic acid O-methylester in 150 ml of toluene was refluxed for 3 h. The
 5 crystals were filtered and washed with toluene. Yield 3.0 g (65%), mp. 235-240 °C.

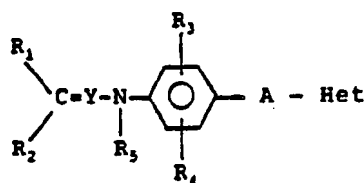
Example 49

5-[2-(4-(1,1-dicyanomethylidenehydrazino)phenyl)ethenyl]-5,6-dihydro-1,3,4-thiadiazin-2(3H)one

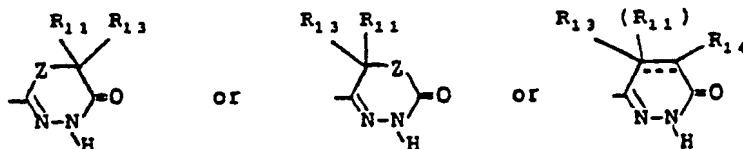
0.4 g of 5-[2-(4-aminophenyl)ethenyl]-5,6-dihydro-1,3,4-thiadiazin-2(3H)one (Example 47) was treated with sodium nitrite and malononitrile as described in Example 1. Yield 0.34 g, mp > 350 °C (decomp).

Claims

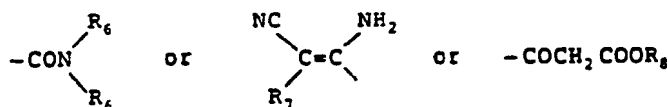
1. New heterocyclic compounds of formula I



wherein Het means one of following groups;

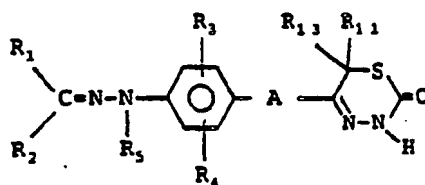


wherein R_{11} , R_{13} and R_{14} mean independently hydrogen or lower alkyl group, Z means S, O or NH; A means valency bond, $-\text{CH}=\text{CH}-$ or $-\text{CH}_2-\text{CH}_2-$ group; R_1 and R_2 independently mean nitro, cyano, halogen, amino, carboxamido, aryl, aroyl, pyridyl, alkoxy carbonyl, acyl or one of following groups;



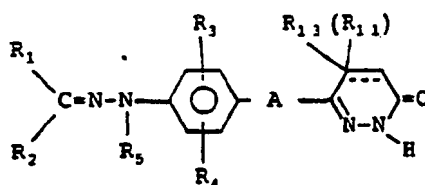
wherein R_6 means hydrogen or lower alkyl group, R_8 means lower alkyl, R_7 means cyano or COOR_{10} , wherein R_{10} means hydrogen or lower alkyl, or R_1 and R_2 together form a substituted or unsubstituted 5 or 6 membered ring which may contain 1 or 2 heteroatom N; R_3 , R_4 , and R_5 mean independently hydrogen, hydroxy or lower alkyl group; Y means N or CH.

2. A compound according to Claim 1 having the structure



wherein R_1 and R_2 mean independently cyano, acetyl, ethoxycarbonyl or carboxamido group and R_3 , R_4 , and R_5 mean independently hydrogen, hydroxy or lower alkyl group, R_{11} and R_{13} mean independently hydrogen or lower alkyl group and A means valency bond or $-\text{CH}=\text{CH}-$ group.

3. A compound according to Claim 1 having the structure



wherein R_1 and R_2 mean independently cyano, acetyl, ethoxycarbonyl or carboxamido group and R_3 , R_4 , and R_5 mean independently hydrogen, hydroxy or lower alkyl group, R_{11} and R_{13} mean independently hydrogen or lower alkyl group and A means valency bond or $-\text{CH}=\text{CH}-$ group.

4. A compound according to Claim 1, which is 6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one

5. A compound according to Claim 1, which is 6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

6. A compound according to Claim 1, which is (E)-6-[2-(4-(1,1-dicyanomethylidenehydrazino)phenyl)-ethenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one

7. A compound according to Claim 1, which is 5-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-5,6-dihydro-6-methyl-1,3,4-thiadiazin-2(3H)one

8. A compound according to Claim 1, which is 5-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-5,6-dihydro-1,3,4-thiadiazin-2(3H)one

9. A compound according to claim 1, which is 6[4-(1,1-diacetylmethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one

10. A compound according to Claim 1, which is 5-[2-(4-(1,1-dicyanomethylidenehydrazino)phenyl)-ethenyl]-5,6-dihydro-1,3,4-thiadiazin-2(3H)one.

11. A compound according to Claim 1, which is 6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydro-5-methyl-1,2,4-triazin-3(2H)one,

12. A compound according to Claim 1, which is 6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydro-1,2,4-triazin-3(2H)one.

13. A compound according to Claim 1, which is

6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]pyridazin-3(2H)one,

6-[4-(1-cyano-1-ethoxycarbonylmethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(1,1-dicyanomethylidenehydrazino)-2-hydroxyphenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(1-cyano-1-(N,N-diethylaminocarbonyl)methylidenehydrazino)-phenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(1-ethoxycarbonyl-1-nitromethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(1-acetyl-1-(N,N-diethylaminocarbonyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(1-ethoxycarbonyl-1-(4-pyridyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(1-bis(ethoxycarbonyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(1-acetyl-1-ethoxycarbonyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(2,6-dioxo-1-cyclohexylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(3,5-dimethyl(4-pyrazolylidenehydrazino)phenyl)-4,5-dihydropyridazin-3(2H)one,

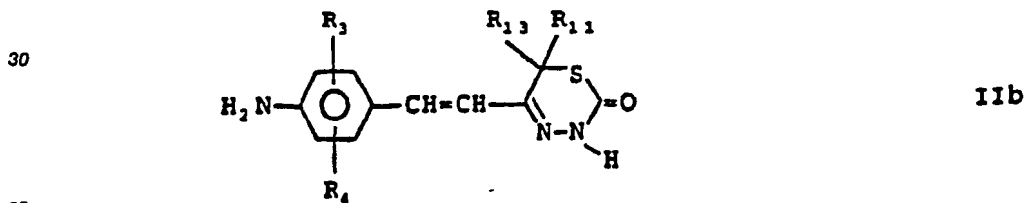
6-[4-(1-acetyl-1-phenylmethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(1-chloro-1-ethoxycarbonyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(1-carboxamido-1-cyanomethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,

6-[4-(1-acetyl-1-benzoylmethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,

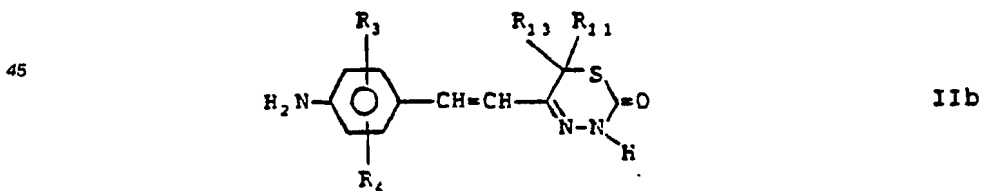
- 6-[4-(1-cyano-1-(2-pyridyl)methylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,
 6-[4-(1,1-diacetylmethylidenehydrazino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one,
 6-[4-(1-amino-1-carboxamidomethylidenehydrazino)phenyl]-4,5-dihydropyridazin-3(2H)one,
 6-[4-(2,2-bis(ethoxycarbonyl)vinyl)aminophenyl]-1,4,5-dihydropyridazin-3(2H)one,
 5 6-[4-(2,2-dicyanovinyl)aminophenyl]-4,5-dihydropyridazin-3(2H)one,
 6-[4-(2,2-diacetylvinyl)aminophenyl]-4,5-dihydropyridazin-3(2H)one,
 6-[4-(1-ethoxycarbonyl-1-ethoxycarbonyl (acetyl)methylidene)-hydrazino)phenyl]-4,5-dihydropyridazin-3(2H)-
 one,
 6-[4-(1,1-dicyanomethylidene-N''-methyl(hydrazino))phenyl]-4,5-dihydropyridazin-3(2H)one,
 10 6-[4-(2-amino-1,1,3-tricyanopropenylidene)hydrazinophenyl]-4,5-dihydropyridazin-3(2H)one,
 6-[4-(1,1-dicyanomethylidene-N''-methyl(hydrazino))phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one,
 6-[4-(2-amino-1,3-dicyano-3-methoxycarbonylpropenylidene)hydrazinophenyl]-4,5-dihydropyridazin-3(2H)-
 one,
 6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydro-4-methylpyridazin-3(2H)one,
 15 2-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-5,6-dihydro-1,3,4-oxadiazin-5-(4H)one,
 (E)-6-[2-(4-(1,1-dicyanomethylidenehydrazino)phenyl)ethenyl]-5-methylpyridazin-3(2H)one,
 6-[2-(4-(1,1-dicyanomethylidenehydrazino)phenyl)ethyl]-4,5-dihydro-5-methylpyridazin-3(2H)one,
 6-[2,5-dimethyl-4-(1,1-dicyanomethylidenehydrazino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one,
 6-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-5-methylpyridazin-3(2H)one,
 20 6-[4-(1,1-dicyanomethylidene-N-methylhydrazino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one,
 6-[4-(1-cyano-1-carbamidomethylidenehydrazino)phenyl]-4,5-dihydro-5-methylpyridazin-3(2H)one,
 4-[4-(1,1-dicyanomethylidenehydrazino)phenyl]phthalazin-1(2H)one or
 2-[4-(1,1-dicyanomethylidenehydrazino)phenyl]-5,6-dihydro-1,3,4-triazin-5(4H)one.
 14. A compound as claimed in any of claims 1 to 13 in the form of a simple salt or acid addition salt.
 25 15. A compound as claimed in claim 14, wherein the salt or ester is pharmaceutically acceptable.
 16. New heterocyclic compounds of formula IIb



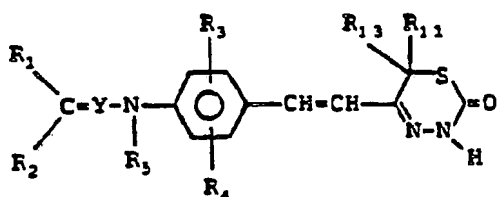
wherein R₃ and R₄ mean independently hydrogen, hydroxy or lower alkyl group and R₁₁ and R₁₃ mean independently hydrogen or lower alkyl group.

17. A compound according to claim 16, which is 5-[2-(4-aminophenyl)ethenyl]-5,6-dihydro-1,3,4-thiadiazin-2(3H)one.

18. The use of a compound of the formula IIb



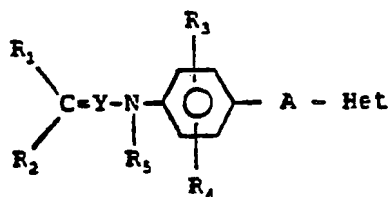
wherein R₃ and R₄ mean independently hydrogen, hydroxy or lower alkyl group and R₁₁ and R₁₃ mean independently hydrogen or lower alkyl group, in preparing of a compound of the formula Ib



Ib

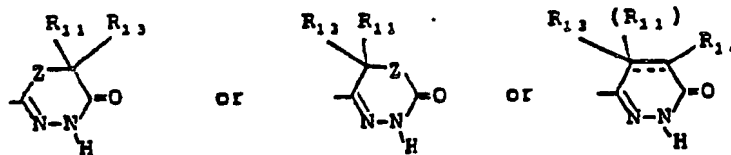
wherein R_1 and R_2 , R_3 , R_4 , R_5 , R_{11} , R_{13} and Y are as defined in Claim 1.

19. A process for the preparation of new heterocyclic compounds of formula I

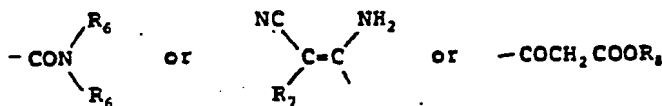


I

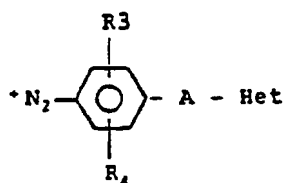
wherein Het means one of following groups;



wherein R_{11} , R_{13} and R_{14} mean independently hydrogen, hydroxymethyl or lower alkyl group, Z means S, O or NH; A means valency bond, $-CH=CH-$, or $-CH_2-CH_2-$ group; R_1 and R_2 independently mean nitro, cyano, halogen, amino, carboxamido, aryl, aroyl, pyridyl, alkoxy carbonyl, acyl or one of following groups;

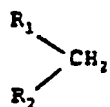


wherein R_6 means hydrogen or lower alkyl group, R_8 means lower alkyl, R_7 means cyano or $COOR_{10}$, wherein R_{10} means hydrogen or lower alkyl or R , and R_2 together form a substituted or unsubstituted 5 or 6 membered ring which may contain 1 or 2 heteroatom N; R_3 , R_4 , and R_5 mean independently hydrogen, hydroxy or lower alkyl group; Y means N or CH, comprising allowing a compound having formula III



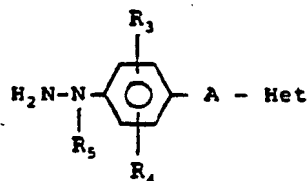
III

wherein R_3 , R_4 , A and Het are the same as defined before, to react with a compound having an activated methylene group of formula IV



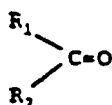
IV

wherein R_1 and R_2 are the same as defined before, in acidic conditions at lowered temperature to give compounds according to formula I or condensating a compound having formula V



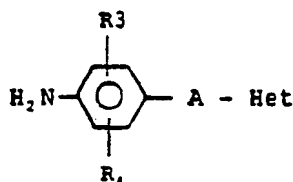
V

wherein R_3 , R_4 , R_5 , A and Het are the same as defined before, with a compound having formula VI



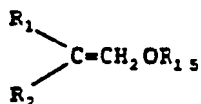
VI

wherein R_1 and R_2 are the same as defined before, in an inert solvent at normal or elevated temperature to give the compounds in accordance with formula I or allowing a compound having formula II



II

wherein R_3 , R_4 , A and Het are the same as defined before, to react with a compound having formula VII



VII

where R_1 and R_2 are the same as defined before and R_{15} is a lower alkyl group in an inert solvent at normal or elevated temperature to form compounds according to formula I where Y is CH, or allowing compounds of formula I where R_5 is hydrogen and Het, A, Y, R_1 , R_2 , R_3 and R_4 are the same as defined before, to react with alkylhalide in an inert solvent and in the presence of an inorganic or organic base to form compounds according to formula I where R_5 is lower alkyl group.

20. A pharmaceutical composition comprising a compound of the general formula I, or a salt or ester thereof, together with a pharmaceutically acceptable carrier.

21. A pharmaceutical composition as claimed in claim 20, in unit dosage form.

22. A pharmaceutical composition as claimed in claim 20 or 21, in the form of coated tablets, dragees, capsules, suppositories, emulsions, suspensions or solutions.

23. A pharmaceutical composition as claimed in claim 20, 21 or 22, additionally including solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners or wetting agents.

(19)



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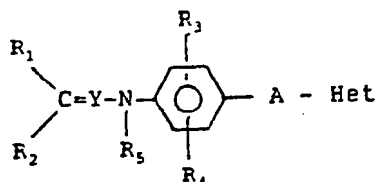
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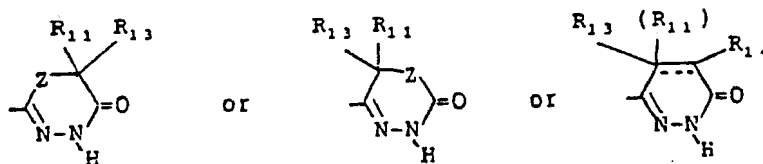
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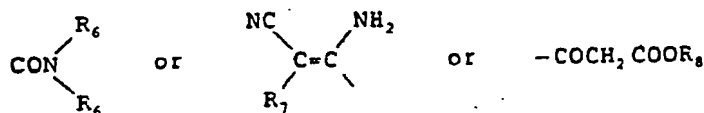
(54) **Heterocyclic compounds.**(57) **New heterocyclic compounds of formula I**

In which Het means one of following groups;

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wherein R_{11} , R_{13} and R_{14} mean independently hydrogen, hydroxymethyl or lower alkyl group, Z means S, O or NH; A means valency bond, $-\text{CH}=\text{CH}-$, or $-\text{CH}_2-\text{CH}_2-$ group; R_1 and R_2 independently mean nitro, cyano, halogen, amino, carboxamido, aryl, aroyl, pyridyl, alkoxy carbonyl, acyl or one of following groups;



wherein R_6 means hydrogen or lower alkyl group, R_8 means lower alkyl, R_7 means cyano or COOR_{10} , wherein R_{10} means hydrogen or lower alkyl or R_1 and R_2 together form a substituted or unsubstituted 5 or 6 membered ring which may contain 1 or 2 heteroatom N; R_3 , R_4 , and R_5 mean independently hydrogen, hydroxy or lower alkyl group; Y means N or CH. The compounds may be used in the treatment of congestive heart failure.



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EUROPEAN SEARCH REPORT

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
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Place of search		Date of completion of search	Examiner
Berlin		19 April 91	KYRIAKAKOU G
CATEGORY OF CITED DOCUMENTS X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons ----- &: member of the same patent family, corresponding document			